REMARKS

STATUS OF THE CLAIMS

Applicants have amended claims 17 and 26. The amendment raises no new issues or new matter as Claim 20 already included the limitation "capsular." Claims 17-28 are pending in the present application and under examination. Claim 29 is withdrawn and claims 1-16 are canceled.

REJECTION OF CLAIMS UNDER 35 U.S.C. § 112, second paragraph

Claims 17-28 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Applicants respectfully traverse the rejection and its supporting remarks.

Claim 26 is clear in scope as the recitation is for "an oligosaccharide from serogroup C *N. meningitidis* (NmC), conjugated to CRM_{197}, and contains from 12 to 22 repeating units from the NmC ***capsular*** polysaccharide" and therefore, the recitation already included the capsular limitation. However, in order to facilitate prosecution in this case applicants have amended pending claims 17 and 26 as suggested by the Examiner, without prejudice or disclaimer.

Applicants respectfully request that the Examiner withdraw the rejection of claims 17-28 under 35 U.S.C. § 112, second paragraph.

REJECTION OF CLAIMS UNDER 35 U.S.C. § 103(a) – 2 References

Claims 17-19, 21-23 and 25 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Constantino *et al.* (*Vaccine* 10:691-698, 1992) in view of Dalseg *et al.* (*Vaccines.* 96. (Ed) Brown F. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., pages 177-182, 1996).

The applicants respectfully traverse the rejection and its supporting remarks. In order to establish a *prima facie* case of obviousness, three criteria must be met: (1) the cited references must teach or suggest all elements of the claimed invention, (2) there must be a teaching or suggestion to modify or combine the references, and (3) there must be a reasonable expectation of success.

1. *No Motivation to Combine*

There is no *prima facie* case of obviousness as there is no motivation to combine. Dalseg *et al.* do not mention oligosaccharides from serogroup C *N. meningitidis* (NmC) conjugated to a carrier and Constantino *et al.* do not mention proteoliposomic vesicles from serogroup B of *N. meningitidis* (NmB). There can be no teaching or suggestion to combine one with the other where they do not mention anything in relation to the other. To remedy this lack, the Examiner has asserted that Dalseg *et al.* provides the motivation to combine asserting that Dalseg *et al.* "expressly taught that meningococcal OMVs have the ability to enhance the antibody responses when coadministered with a microbial antigen locally as well as at distant mucosal sites." Applicants respectfully disagree with this assertion. Dalseg *et al.* only taught that taught that meningococcal OMVs have the ability to enhance the antibody responses when coadministered with a formalin-inactivated influenza virus. It is highly speculative to extrapolate this one example to a generalization of wide utility. Dalseg *et al.* expressly acknowledge this as speculative in their conclusions, "It is likely that OMV ***might*** exert its function by acting as a carrier through the mucosal membranes and that it ***might*** be useful as a mucosal adjuvant for several nonproliferating microbial antigens." Thus, Dalseg *et al.* do not provide a suggestion to use their meningococcal OMVs as an adjuvant with oligosaccharides from serogroup C *N. meningitidis* (NmC) conjugated to a carrier. Further, Constantino *et al.* do not provide any suggestion to use meningococcal OMVs as an adjuvant with their oligosaccharides. Notably, Constantino *et al.* on page 693, first column, "Vaccines," teach the use of aluminum hydroxide, which is an adjuvant. In addition, Constantino *et al.* do not even discuss any insufficiency of the antibody response observed as a problem that might motivate one of skill in the art to even try other adjuvants. Constantino *et al.* not only do not suggest a lack of antigenicity that would require an adjuvant, Constantino *et al.* already have an adjuvant. The Examiner has therefore suggested use of Dalseg *et al.* to solve a problem that does not exist.

2. *Inappropriate Obvious to Try*

Even if one of skill in the art were motivated to add yet another adjuvant to the oligosaccharide composition of Constantino *et al.*, this is at best a suggestion that it would be obvious to try among all the available adjuvant to determine which, if any, would work synergistically with aluminum hydroxide or better than aluminum hydroxide. The Federal Circuit in *In re O'Farrell* stated that:

> "The admonition that 'obvious to try' is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave no indication as to which of many possible choices is likely to be successful.... In others, what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidelines as to the particular form of the claimed invention or how to achieve it." In re O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988).

Thus, if one of skill in the art was motivated to increase the antigenicity by adding a second adjuvant to the composition of Constantino *et al.*, the person of ordinary skill in would try from a large number of available adjuvants. By way of example, U.S. Pat. No. 6,638,513 from col. 12, line 37 to col. 13, line 2 (cited by the Examiner on page 7 of the Office Action sent on May 1, 2006) identifies at least six classes of adjuvants that includes seventeen different adjuvants.

> Adjuvants may also be used to enhance the effectiveness of the vaccines. Adjuvants can be added directly to the vaccine compositions or can be administered separately, either concurrent with or shortly after, vaccine administration. Such adjuvants include, but are not limited to: (1) aluminum salts (alum), such as aluminum hydroxide, aluminum phosphate, aluminum sulfate, etc.; (2) oil-in-water emulsion formulations (with or without other specific immunostimulating agents such as muramyl peptides (see below) or bacterial cell wall components), such as for example (a) MF59 (International Publication No. WO 90/14837), containing 5% Squalene, 0.5% Tween 80, and 0.5% Span 85 (optionally containing various amounts of MTP-PE (see below), although not required)

formulated into submicron particles using a microfluidizer such as Model 110Y microfluidizer (Microfluidics, Newton, Mass.), (b) SAF, containing 10% Squalane, 0.4% Tween 80, 5% pluronic-blocked polymer L121, and thr-MDP (see below) either microfluidized into a submicron emulsion or vortexed to generate a larger particle size emulsion, and (c) Ribi.TM. adjuvant system (RAS), (Ribi Immunochem, Hamilton, Mont.) containing 2% Squalene, 0.2% Tween 80, and one or more bacterial cell wall components from the group consisting of monophosphorylipid A (MPL), trehalose dimycolate (TDM), and cell wall skeleton (CWS), preferably MPL+CWS (Detox.TM.); (3) saponin adjuvants, such as Stimulon.TM. (Cambridge Bioscience, Worcester, Mass.) may be used or particle generated therefrom such as ISCOMs (immunostimulating complexes); (4) Complete Freunds Adjuvant (CFA) and Incomplete Freunds Adjuvant (IFA); (5) cytokines, such as interleukins (IL-1, IL-2, etc.), macrophage colony stimulating factor (M-CSF), tumor necrosis factor (TNF), etc.; and (6) other substances that act as immunostimulating agents to enhance the effectiveness of the composition.

Muramyl peptides include, but are not limited to, N-acetyl-muramyl-L-threonyl-D-isoglutamine (thr-MDP), N-acteyl-normuramyl-L-alanyl-D-isogluatme (nor-MDP), N-acetylmuramyl-L-alanyl-D-isogluatminyl-L-alanine-2-(1'-2'-dipalmitoyl-sn -glycero-3-huydroxyphosphoryloxy)-ethylamine (MTP-PE), etc.

Thus, from this list alone, one of skill in the art would have eighteen adjuvants (including the adjuvant identified by the Examiner) to test to see which may increase the antigenicity of the composition of Constantino *et al.* beyond the adjuvant already in the composition.

3 *No reasonable expectation of success*

Even if Dalseg *et al.* could be read as teaching or suggesting some reason that it would be desirable to combine with the teachings of Constantino *et al.*, one of skill in the art would not have a reasonable expectation of success. Support for this assertion may be found in the text of Dalseg *et al.* itself. As noted above, Dalseg *et al.* state that the OMVs only ***might*** be useful as an adjuvant for microbial antigens with only a demonstration that it works for one. Thus, the very reference that the Examiner has asserted to provide a motivation to combine states recognizes the

uncertainty of using the OMVs as an adjuvant with other antigens, indicating that one of skill in the art would not have a reasonable expectation of success. Furthermore, the present application actually *proves* that the effect of OMVs as an adjuvant is unpredictable. Figure 2B compares the efficacy of MenC conjugate alone (number 1) with the efficacy of the combined MenC conjugate and MenB OMV (number 4) after the first and second vaccinations. From this figure, it is clear that contrary to the Examiner's assertion that addition of MenB OMV would act as an adjuvant to increase the antigenicity of the MenC conjugate, the MenB OMV actually slightly decreases the antigenicity of the MenC conjugate, though not enough to render the MenC conjugate ineffective. Thus, not only is there uncertainty in the result, the actual combination in fact fails to produce the result of increased antigenicity.

Applicants therefore respectfully request that the Examiner withdraw the rejection of claims 17-19, 21-23 and 25 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Constantino *et al.* in view of Dalseg *et al.* First, there is no motivation to combine as the composition of Constantino *et al.* already has an adjuvant. Second, even if there were a motivation to add a new adjuvant to Constantino *et al.*, there are many available adjuvants, so at best it would merely be obvious to try all of them to see which one provides the optimal result (and the present application proves that the composition of Dalseg *et al.* in fact does not work). Third, there is no reasonable expectation of success given that Dalseg *et al.* themselves teach the uncertainty of the utility of their OMVs as an adjuvant (and again the present application proves that the composition of Dalseg *et al.* in fact does not work).

REJECTION OF CLAIMS UNDER 35 U.S.C. § 103(a) – 3 References

Claims 17-19, 21-23 and 25 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Constantino *et al.* (*Vaccine* 10:691-698, 1992) and Dalseg *et al.* (*Vaccines.* 96. (Ed) Brown F. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., pages 177-182, 1996) in view of Paradiso *et al.* (*Dev. Biol. Stand.* 87: 269-275, 1996)

The applicants respectfully traverse the rejection and its supporting remarks. In order to establish a *prima facie* case of obviousness, three criteria must be met: (1) the cited references must teach or suggest all elements of the claimed invention, (2) there must be a teaching or suggestion to modify or combine the references, and (3) there must be a reasonable expectation of success.

1. *No Motivation to Combine*

There is no *prima facie* case of obviousness as there is no motivation to combine. As discussed above, Dalseg *et al.* do not mention oligosaccharides from serogroup C *N. meningitidis* (NmC) conjugated to a carrier and Constantino *et al.* do not mention proteoliposomic vesicles from serogroup B of *N. meningitidis* (NmB). There can be no teaching or suggestion to combine one with the other where they do not mention anything in relation to the other. To remedy this lack, the Examiner has asserted that Paradiso *et al.* provides the motivation to combine, specifically citing to the following paragraph bridging pages 272 and 273:

> A significant portion of the morbidity from meningococcus is caused by group B. Unfortunately, the capsule from group B is not very immunogenic in people because of the similarity to saccharide structures on human cells. For this reason, and because of the potential for anti-group B antibody to cross-react with brain tissue, alternative approaches have been sought. Most of the work has been done on outer membrane vesicles prepared from cells of virulent group B strains [10]. It seems likely that in the future it will be desirable to mix such a vaccine with the group C and/or group A conjugates. Since these vesicle preparations contain an array of proteins and lipids, the combinations ***will create a new set of formulation challenges*** not unlike those encountered in mixing conjugate vaccines with DTP. [emphasis added]

A motivation to combine must suggest the desirability of making the combination otherwise it's not a ***motivation***. As discussed in the response submitted on January 9, 2006, Paradiso *et al.* do not cite to a reason that would motivate one of skill in the art to combine the references. Rather, Paradiso *et al.* suggest that in the future there may be some uncited reason that it would be desirable. Further, in the very next sentence, Paradiso *et al.* state that there ***will*** be challenges to formulation of such a combination. Therefore, Paradiso *et al.* teach that there is no motivation today, but at best there

may be a motivation in the future and that those of skill in the art will face difficulties at such future time in making the combination.

In addition, the cited motivation in Paradiso *et al.* is to mix outer membrane vesicles prepared from cells of virulent group B strains as a vaccine component while Dalseg *et al.* teach outer membrane vesicles as an ***adjuvant*** for formalin-inactivated influenza virus, not as a vaccine component as is asserted by the Examiner on page 5 of the Office Action sent 5/1/06. Dalseg *et al.* only present data regarding the antigenicity of the formalin-inactivated influenza virus and do not look at whether the OMVs produce any immune response to MenB. Thus, the cited motivation in Paradiso *et al.* is at odds with cited motivation in Dalseg *et al.* and Dalseg *et al.* do not teach that the OMV was actually itself antigenic when combined with formalin-inactivated influenza virus. Further, the addition by the Examiner of Dalseg *et al.* does not bolster the rejection by supplementing with a second motivation of use of OMVs as an adjuvant. As discussed above, there is no motivation to add yet another adjuvant to the composition of Constantino *et al.* and even if there were, there would be no reasonable expectation of success, especially in light of the fact that the MenB OMVs simply fail to provide an adjuvant effect in combination with the MenC conjugate.

2. *No Reasonable Expectation of Success*

Even if Paradiso *et al.* could be read as teaching or suggesting some reason that it would be desirable to combine the teachings of Constantino *et al.* and van der Voort *et al.*, one of skill in the art would not have a reasonable expectation of success. Support for this assertion may be found in the text of Paradiso *et al.* itself. As noted above, Paradiso *et al.* state that there ***will*** be challenges, not that there might be difficulties. Thus, the very reference that the Examiner has asserted to provide a motivation to combine states that there will be challenges that must be overcome, indicating that one of skill in the art would not have a reasonable expectation of success. Furthermore, Paradiso *et al.* provide data in Table 5 on page 273 comparing a multivalent vaccine with separate application of the individual vaccine components. As discussed by Paradiso *et al.* on page 273, certain of the components produced a weaker immune response in the multivalent vaccine and certain components produced a stronger immune response in the multivalent vaccine. Thus, in

addition to stating that there will be difficulties that need to be overcome, Paradiso *et al.* also teach that there is unpredictability in combining vaccine components into a multivalent vaccine. Each fact alone would prevent one of skill in the art from having a reasonable expectation of success in combining the teachings of Constantino *et al.* and van der Voort *et al.*, but together, there certainly could not be a reasonable expectation of success until the present inventors have actually taught that the combination in fact does work as they do in the present application.

Further, as discussed above Dalseg *et al.* not only does not provide a reasonable expectation of success for the second motivation, the combination simply does not provide the adjuvant effect as suggested by the Examiner.

The Examiner has cited to a number of references in support of the assertion that proteosomic group B meningococcal outer membrane vesicles have been routinely mixed with other microbial antigens in a vaccine with no formulation challenges. However, none of the references cited actually support this assertion. Lowell *et al.* (US 6,476,201) do not teach novel formulations of multivalent vaccines. Lowell *et al.* ('201) teach a modified technique for mixing different components of previously formulated multivalent vaccines (see, for example, the abstract). Since Lowell *et al.* ('201) are merely applying a modified manufacturing technique to previously developed formulations, it is entirely expected that they would not mention difficulties in generating the formulations. Thus, Lowell *et al.* do not address whether it is uncertain to formulate multi-component vaccines.

Lowell *et al.* (*J. Exp. Med.* 167: 657-663, 1988) is not relevant either as it only looks at use of the OMV proteostomes as a conjugate carrier to increase antigenicity. Lowell *et al.* did not look at whether the OMV proteostomes produced an immune response that induced antibodies to MenB. Thus, this paper only looks at use of the OMV proteostomes as an adjuvant and not as a second component in a multi-component vaccine. And as discusses above, the use of OMVs as an adjuvant is clearly unpredictable as the OMVs did not increase the antigenicity of the MenC oligosaccharides. Thus, Lowell *et al.* do not address whether it is unpredictable to formulate multi-component vaccines.

From Zollinger *et al.* (US 6,558,677), the Examiner cited to the first full paragraph in column 8, which states:

> The LPS of a number of Gram negative pathogens has been identified as a dominant antigen capable of inducing protective antibodies, but it is typically a poor immunogen by itself. Thus ***efforts have been made*** to covalently conjugate the LPS to a carrier protein or non-covalently complex the LPS to proteosomes in order to enhance its immunogenicity. In these cases the use of NOMV prepared from the homologous pathogen ***may*** be a highly effective solution to the problem of increasing the LPS immunogenicity.

Again, Zollinger *et al.* are not suggesting use of the NOMV as a component in a multi-component vaccine, but rather the use as an adjuvant to increase immunogenicity. Zollinger *et al.* did not actually combine their NOMV with a bacterial LPS to see if it could, in fact, increase the antigenicity of the LPS, but rather only speculated that it ***may*** serve the role as an adjuvant. Further, they only cite to efforts to conjugate LPS with proteostomes without citing to actual successes. Thus, Zollinger *et al.* do not address whether it is unpredictable to formulate multi-component vaccines and did not even demonstrate that the NOMV or other proteostomes function as adjuvants.

Finally, Poolman *et al.* (*Antonie van Leeuwenhoek* 53:413-419, 1987) were not looking at combining two vaccine components into a multicomponent vaccine. The Lipooligosaccharide (LOS) was merely added to remove the detergent. It is worth noting that the LOS was the polysaccharide, which is less much antigenic than the capsular oligosaccharide. Further, the LOS is not conjugated to a carrier which means it is even more poorly antigenic. Finally, the LOS was only 5% by weight of the OMPs (see page 415, first full paragraph) whereas the capsular oligosaccharide conjugate is in 1:2.5 ratio with the NmB proteoliposomic vesicles in the Examiners (See page 2, Example 1 of the specification). Thus, it is unlikely that the LOS was even acting as either an adjuvant or a second antigenic component. Finally, Poolman *et al.* teach that adding the vaccine without the LOS "tends to induce a higher and more rapid bactericidal antibody response as compared to the [LOS containing] vaccine." One of skill in the art would expect that switching to a ten-fold higher amount of an antigenic capsular oligosaccharide would further reduce the antigenicity of the OMVs. Thus, Poolman *et al.* actually teaches against the claimed composition.

Strangely enough though, Figure 2A of the specification shows that the opposite actually happens, the MenB OMVs alone produce a slightly lower bactericidal response than the combination with the MenC conjugate.

None of the references cited by the Examiner support the assertion that formulating multi-component vaccines is routine because none of them look at novel formulations of multicomponent vaccine. One of them even teaches away from the presently claimed composition. The references either discuss mixtures of adjuvants and antigens or new ways of manufacturing existing formulations.

3. *References Teach Away*

Even if a *prima facie* case of obviousness has been established, a *prima facie* case may be rebutted where there is evidence of teaching away. Teaching away may come in the form of a reference criticizing, discrediting or otherwise discouraging the solution claimed. Paradiso *et al.* clearly teach away from combining the teachings of Constantino *et al.* and van der Voort *et al.* in three ways. As discussed above, Paradiso *et al.* talk of a future desirability which implies that there is no reason at present to make the combination. Paradiso *et al.* also talk of challenges that must be overcome before such combination would actually work. Paradiso *et al.* also show that the results of combining vaccines are unpredictable, which suggests that such combination may never work. All three of these teachings would discourage one of skill in the art from attempting the presently claimed invention.

Applicants therefore respectfully request that the Examiner withdraw the rejection of claims 17-19, 21-23 and 25 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Constantino *et al.* and Dalseg *et al.* in view of Paradiso *et al.* as there is no motivation to combine the references and no reasonable expectation of success for such combination, and even if there were both, Paradiso *et al.* teach away from the claimed invention by discouraging one of skill in the art from attempting the combination.

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REJECTION OF CLAIMS UNDER 35 U.S.C. § 103(a) – 4 References

Claim 24 has been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Constantino *et al.* (*Vaccine* 10:691-698, 1992) as modified by Dalseg *et al.* (*Vaccines.* 96. (Ed) Brown F. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., pages 177-182, 1996) and Paradiso *et al.* (*Dev. Biol. Stand.* 87: 269-275, 1996) as applied to claim 17 above, and further in view of Seid (US 6,638,513).

Applicants respectfully traverse the rejection and its supporting remarks. As discussed above regarding the preceding two obviousness rejections, Constantino *et al.*, Dalseg *et al.*, and Paradiso *et al.* fail to render the invention of claim 17 obvious because collectively they fail to provide a motivation to combine, they fail to provide a reasonable expectation of success, and Paradiso *et al.* actually teaches away from the combination by citing to difficulties that will need to be overcome. Seid fails to overcome any of these deficits as Sied is directed to oligosaccharides from serogroup B of *N. meningitidis* and therefore could not provide a motivation to combine, nor a reasonable expectation of success in combining, oligosaccharides from serogroup C *N. meningitidis* (NmC) conjugated to a carrier and proteoliposomic vesicles from serogroup B of *N. meningitidis* (NmB).

Applicants therefore respectfully request that the Examiner withdraw the rejection of claim 24 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Constantino *et al.* as modified by Dalseg *et al.* and Paradiso *et al.* as applied to claim 17 above, and further in view of Seid as there is no motivation to combine the references and no reasonable expectation of success for such combination, and even if there were both, Paradiso *et al.* teach away from the claimed invention by discouraging one of skill in the art from attempting the combination.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

Please direct all further written communications regarding this application to:

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In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. **03-1952** referencing docket no. **223002100100**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: November 1, 2006

Respectfully submitted,

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